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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/030,417 | 08/14/2002 | Rainer H Muller | 668-59190 | 8775 |

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| EXAMINER | |
|---|---|
| BERKO, RETFORD O | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1615 | |

DATE MAILED: 08/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/030,417 | MULLER ET AL. | |
| | Examiner | Art Unit | |
| | Retford Berko | 1615 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *22 August 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/18/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

Acknowledgement: The Information Disclosure Statement filed and amendment of claims August 22, 2002 is acknowledged.

### Status of Claims

According to ART 34 AMDT, claims 1-27 are pending.

### Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1-4, 7, 10, 11, 13, 15, 22 and 27 are rejected under 35 U.S.C. 102(e) as being anticipated by Muller et al (US 5, 858, 410; filed May 23, 1996).

The claims are drawn toward a process for preparation of microparticles and nanoparticles of drug (particle size or diameter equal to 1-5.6 microns or less); the method comprising of high-pressure homogenization in a piston-gap homogenizer in an anhydrous or

water-reduced medium at low temperature (e.g. room temp or at less than 90 degrees), with minimal impairment of stability. Specified drugs include paclitazel, prednisolone or carbamazepine and the homogenized matrix is a polymer material (semi-synthetic or natural). The claims are also directed toward dispersion of the drug in a non-medium (e.g. polyethylene glycol) and the process is conducted at temperatures above 20, preferably below 50 or particularly below 30 degrees.

As in applicant's claims 1-4, Muller et al (Patent '410) teaches a method for preparing nanoparticles of drugs (e.g. corticoids such as prednisolone---see col 22, lin 40-45); the drug particles having average size of 10-1, 000 nanometers by dispersing solid therapeutically active drugs in a solvent and subjecting the dispersion to high pressure homogenization in a piston-gap homogenizer (abstract and col 20, lin 23-30) at room temperature (col 18, lin 10-20 and col 20, lin 35-40).

Also, as in claim 4 and 7, according to Muller et al, the drug matrix or carrier can be a polymer such as polyethylene glycol (col 19, lin 65).

Patent '410 teaches all the limitations in claims10, 13 and 15, 22 and 27 because in the process described, nanosuspensions of microparticles of drugs in viscous dispersion media are prepared (col 3, lin 20-25 and col 20, lin 5-10) after the insoluble or moderately soluble drugs have been dissolved in organic solvent at room temperature (col 20, lin 35-40).

Patent '410 teaches the use of the limitations in claims 11 and 13 because the carrier in which drug particles are dispersed include the mono or di or triglycerides and polyethylenen glycol (col 19, lin 60-65).

Claims 1-4, 7, 10, 11, 13, 15, 22 and 27 are anticipated by ' 410.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-27 are rejected under 35 U.S.C.103(a) as being unpatentable over Desai et al (WO 98/14174).

The claims are drawn toward a process for preparation of microparticles and nanoparticles of drug (particle size or diameter equal to 1-5.6 microns or less). The method comprises of high-pressure homogenization in a piston-gap homogenizer in an anhydrous or water-reduced medium at low temperature (e.g. room temp or at less than 90 degrees), with minimal impairment of stability. The claims are directed towards specified drugs (e.g. paclitazel, prednisolone or carbamazepine) and the homogenized matrix material is a polymer such as polylactide/glycolide co-polymer (semi-synthetic or natural). The claims are also directed toward dispersion of the drug in a non-medium (e.g. polyethylene glycol) and the process is conducted at temperatures above 20, preferably below 50 or particularly below 30 degrees. The

claims are further directed toward the process wherein the homogenized matrix material is a polysaccharide or a natural macromolecule.

Desai et al (Patent WO '174) discloses a process for preparation of microparticles or nanoparticles of water insoluble drugs; e.g. paclitazel, an agent that is insoluble in water. The drug is dissolved in an organic solvent (page 17, lin 15-25); a protein such as albumin is added to stabilize the nanoparticles (page 17, lin 31-34) and the mixture is homogenized under high pressure homogenization (page 18, lin 6-15 and page 51, lin 25). In disclosing a method for making a pharmaceutically acceptable formulation, WO '174 discusses sterile-filtration and how drug of particle size less than 200 nm is obtained (page 19, lin 1-16 ; page 10, lin 24 and page 20, lin 30-35). According to Desai, the drug particles can be in crystalline or amorphous for (page 13, lin 5-10): details of how to make drug particles of size less than 200 nm are provided. Furthermore, Desai et al also disclose the effect the solvent used has on drug particle size (page 38, lin 5-20) and further discuss the advantage of making the composition in the form of albumin-paclitazel combination—low toxicity.

One of ordinary skill in the art would be motivated to make paclitazel or itraconazole compositions according to the methods disclosed in the cited prior art wherein the methods have been shown to provide advantages of reduced volumes and low toxicity products. One of ordinary skill would expect to obtain economic advantage of making stabile aqueous suspensions of water-insoluble drug such as paclitazel in ready-to-use formulation while maintaining low toxicity of the drug in humans. Therefore the invention as a whole would have been prima facie obvious to one of ordinary skill at the time the invention was made.

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**Correspondence**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Retford Berko** whose telephone number is 703-305-4442. The examiner can normally be reached on M-F from 8.00 am to 5.30 pm

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Thurman K Page**, can be reached on 571-272-0602. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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